MIGRAINE AND ITS TREATMENT

HENRY ALSOP RILEY
Professor of Neurology, College of Physicians and Surgeons

Migraine, or "sick headache," as it is often called may be defined as a recurrent headache, usually unilateral, often incapacitating in severity, culminating in nausea or vomiting, frequently accompanied by evidences of disturbance in various parts of the brain, occurring against a background of relatively good health and associated with a familial history of headache, convulsions or other paroxysmal disorders. While this definition is quite satisfactory for the great majority of cases, it need not be considered as an absolutely rigid one since many deviations from these criteria may occur. A gradual broadening of the concept of migraine has taken place during the last twenty years introducing a considerable degree of elasticity into the limitations of the disorder. This has resulted in the grouping together of a considerable number of signs and symptoms as a symptom-complex called migraine. No case will present all of the symptoms and signs of this syndrome and one or more of the important cardinal manifestations may fail to appear. On account of the significant grouping of subordinate evidences of disturbance the absence of important symptoms need not invalidate the diagnosis of migraine and even the cardinal symptom, headache, may be insignificant or absent.

The diagnosis of migraine requires a thorough physical examination and in many instances comprehensive study by all the available means of laboratory diagnosis. Such an examination often demonstrates a physical basis for the symptoms and in such instances, the diagnosis of a symptomatic migraine may be made.

This type of the disorder may be found to depend upon uncorrected refractive errors, sinus diseases, severe secon-

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dary anemia, nephritis, serious disease of the gastro-intestinal tract and its appendages, particularly the liver, intoxications—such as lead, gout or other exogenous and endogenous poisons and many miscellaneous conditions. A careful neurological examination may demonstrate the presence of a neoplasm of the brain affecting specialized areas or structures, internal hydrocephalus, tabes, cerebral arteriosclerosis or cerebral edema. If these systemic and organic neurological conditions have been eliminated as productive of the symptom-picture one is then faced with the determination whether or not the headache may be caused by psychogenic factors. This distinction is often difficult and sometimes impossible. The study of psychogenic disorders in the vast majority of instances shows that the patient is achieving or accomplishing something by means of the illness. The asset value of psychogenic disorders must always be borne in mind. The evaluation of the many factors bearing upon this phase of the situation requires a careful and painstaking history, concerning not only the intimate character of the headache and the patient but also the more remote social, economic, familial and other environmental features. It is rare indeed that this type of patient is found to present a monosymptomatic complaint. Many other indications of the underlying conflict which forms the basis for the symptom-picture may be discovered in addition to the presenting symptoms. In general, these evidences of disordered function fall into the category of the hysterical or conversion symptoms by which physical manifestations serve as the external indications of mental conflicts. These disorders may appear as disturbances in any of the general or special sensory or motor spheres. The majority of psychogenic disorders cannot be explained upon the basis of the anatomy and physiology of the nervous system. Conflicting symptoms appear and many important manifestations which should accompany the evidences of real disorders of the nervous system fail to make their appearance. The attitude of the patient, his contact with the physician, his behavior during the examination, and the general impression

gained from an estimate of his story and his presentation of it are often the most important factors leading to a correct clinical evaluation of the situation.

With the elimination of the symptomatic and functional types of migraine one is able to arrange the remaining cases in certain fairly well defined sub-groups. It must be remembered, however, that migraine has as yet no definitely established individuality and that it presents features which ally it with a whole galaxy of clinical disorders including such dissimilar clinical entities as the paroxysmal disorders and familial periodic paralysis. Variations in its manifestations, alternations from one sub-group to another or transitions between one or another of the more closely related disorders are so frequently met with that the majority of investigators consider the symptoms as the expression of an underlying tendency capable of producing a highly diversified syndrome.

With the growing appreciation of the ramifications of the disorder, many investigators influenced by the theory of the reflex causation of the symptoms endeavored to differentiate groups such as ear, eye, gastric and genital types according to the supposed identification of reflexogenous zones operative in the individual case. The possibility for clinical confusion upon such an etiological basis is infinite. The more accurate grouping of cases according to etiological factors will have to await a more intimate knowledge of the disorder.

It is open to considerable doubt whether all of the types now grouped under the caption migraine rightly belong there. It is highly possible that some of the types have been incorrectly included under this heading. The final determination of these facts will have to await a greater knowledge of the mechanism of the disorder.

Due to our ignorance of the fundamental causes and factors which underlie the manifestations of this disorder the differentiation into types must be based upon clinical

criteria and such a division for descriptive reasons serves a definite purpose.

The occurrence of this disorder in many individuals is characterized by a definite and often stereotyped appearance and course. These relatively constant symptomatic manifestations make it possible to determine a certain number of well recognized types.

Simple Migraine or Hemicrania

This is the simplest type and by far the most frequent. It is characterized by a unilateral headache of varying severity which usually is followed by nausea, and in severe cases, by vomiting. It may be associated with certain prodromal symptoms which warn the patient of the impending attack but it usually is not followed by any sequelæ and within a relatively short time after the cessation of the headache the patient returns to a state of normal comfort.

Ophthalmic Migraine

This type of the disorder is characterized by symptoms which affect the visual function. The manifestations of ophthalmic migraine are somewhat more irregular in their course and development than those of simple migraine. There may be only one or two attacks during an entire lifetime or the symptoms may occur every day. The association of ophthalmic migraine with other distinctly paroxysmal or convulsive disorders is perhaps somewhat closer than in simple migraine, occurring in about 7.2 per cent of cases. The paroxysmal manifestations usually consist of petit mal attacks, twilight states or typical convulsive seizures.

The disturbances in vision may vary tremendously in character and in degree. The distribution of the disturbance may be limited, affecting a part of the field of vision of one eye alone, it may be homonymous, or it may result in an obscuration or loss of vision in both eyes. It may consist of little more than a fine cloud or a single colored shimmering effect. In many instances it may appear as a black, dull-colored or shining spot which, either motionless

or moving about, gradually increases in size until it occupies a definite part of or the whole of the visual field. A simple transitory amblyopia may appear, first as a clouding of vision, then a complete amaurosis which finally disappears without any sequelæ. In many instances a shimmering, wave-like or vibrating distortion of the appearance of objects, may take place. The most characteristic manifestation is the scintillating scotoma which usually appears in a circumscribed area of the visual field, often presenting an homonymous distribution. It consists of jagged, straight, zigzag or irregular bands of light, often in movement, less often stationary. It frequently presents itself as the so-called "fortification figures" in which the center of the visual hallucination is a scotoma surrounded by a jagged or vermicular band frequently consisting of several colors. These manifestations, considered to be irritative, are gradually replaced by paralytic phenomena, a scotoma appearing in the field previously affected by the scintillation. This scotoma may be either relative or absolute depending upon the degree of the disturbance. It persists for a variable length of time. The characteristic headache usually appears as the irritative or paralytic manifestations of the disorder fade away and may be mild, severe or incapacitating. It is usually followed by nausea and vomiting. The ophthalmic type is often followed by definite sequelæ usually as a scotoma which may last for a variable length of time. Where the disturbance is extremely severe or frequently repeated, the recurrent scotoma may become fixed with a permanent loss of vision.

Psychic Migraine

This form of the symptom-complex has been described by various investigators and sufficient corroboration of their observations has been recorded to justify the establishment of a definite type of psychic alteration associated with periodic headache. It has, however, been attacked by other investigators and is perhaps not so firmly substantiated as the simple and the ophthalmic types. There are not, however, the definite objections to it which can be raised

in the case of the facioplegic and the ophthalmoplegic types of migraine. The mental disorder seemed so definite and characteristic to one investigator, that he originated and used the term "dysphrenia hemicrania transitoria" to describe the disturbed psychic state. Psychic involvement in the course of migraine usually appears as a twilight state in which the patient is confused, disoriented as to place and time with occasional hallucinations of sight and hearing. These hallucinations may attain a marked degree of clarity. Acts of violence, including suicide and murder, have been perpetrated in the migrainous psychotic state. This aspect of the disorder has been considered of such importance that it has been stated that in any crime characterized by instantaneousness, fierceness and brutality, careful search must be made in the personal and family history of the patient for paroxysmal headaches or convulsions, the supposition being that the acts of violence may represent crimes committed by an individual not in the proper control of his psychic activities.

Emotional disturbances with changes in mood, and a feeling of depression quite commonly accompany or follow the headache. These may go on to a misanthropic, asocial, introspective type of reaction. There is frequently a weakness in the mental processes with distractibility and some incoherence. Certain other patients present disturbances of the manic-depressive type in which there may be restlessness, irritability, change of personality, alternating with depression and retardation of psychomotor activity.

Psychic equivalents have been described by numerous writers in which temporary disturbances of the psychic sphere may alternate with definite attacks of migraine. These episodes are characterized principally by depression, a feeling of strangeness, confusion, absent-mindedness and a sense of unreality. Whether these and other similar manifestations can be attributed to the same type of disturbance which underlies the other features of migraine may, perhaps, be open to some doubt. It would seem justifiable tentatively to include the psychic form of migraine and

the psychic equivalents as integral constituents of the migraine syndrome and await further investigation for absolute justification as to their existence and inclusion in the symptom-picture.

Abdominal Migraine

For many years, attacks of recurrent pain apparently without cause and unassociated with any demonstrable disease of the intra-abdominal organs has been a matter of considerable interest and perplexity to physicians. The clue to the essential character of some of these attacks of abdominal pain was furnished by the observation that they were associated with or followed by typical migrainous headaches. Due to the discovery of this association a type of migraine has been described as "abdominal migraine." The attack is characterized by pain which is variously complained of as cutting, boring or grinding and situated anywhere within the abdomen but usually in the epigastrium. In a certain number of instances these crises of abdominal pain may take place without the headache. The abdominal pain is usually associated with nausea, vomiting and diarrhœa. No further evidence of disturbed function of the abdominal organs can be elicited by physical examination. In certain instances abdominal migraine may alternate with typical attacks of migraine or a simple migraine may gradually be transformed into the abdominal type of the disorder. In many instances the family history is of considerable value in establishing the diagnosis. Either migraine itself, various manifestations of the convulsive state, certain exudative disturbances of the skin or asthma may be discovered in members of the same generation or in the familial history of the patient. A sufficient number of carefully observed cases has already been reported to supply a firm basis for the recognition of the abdominal type of the disorder.

In line with the identification of the abdominal type of migraine certain authors have described a thoracic type which is characterized by disorders of the heart and lungs.

Recorded instances of this type have been relatively few in number. Cases of paroxysmal tachycardia have been reported with associated severe headache of a migrainous character. Certain disorders of the pelvic organs characterized by sudden forced evacuation of the bowels or bladder, disturbances of the genital organs; associated with severe headache, nausea and profuse perspiration have been described as a pelvic type of migraine. At the present time it is perhaps inadvisable to establish a thoracic or pelvic type of migraine since the number of reported cases is relatively insignificant but the possibility of this sort of a disturbance should always be borne in mind in connection with vague obscure thoracic or pelvic symptoms associated with a migrainous headache.

An abortive type of migraine has also been described in which various prodromal symptoms appear, continue for a variable length of time and then disappear without the development of a severe headache or other manifestations of the disorder.

There are two varieties accepted in the past under the heading of migraine which may be seriously questioned, the ophthalmoplegic and the facioplegic types. The ophthalmoplegic type of migraine is characterized by weakness, usually transient, of one or more of the oculomotor nerves. The third cerebral nerve is the one usually affected The disturbance may be total or the involvement of the nerve may be a differential one, affecting only certain parts of the nerve. In rarer instances the trochlear or abducens nerve may be affected by the disturbance in function.

A number of features of the ophthalmoplegic type of migraine may be cited to demonstrate that this form of the disorder is somewhat different from the other types. The age range is greater, individuals as young as two years of age and as old as fifty having been afflicted with disturbances of the oculomotor nerves. There is a well defined type of recurrent oculomotor paralysis which is not associated with headache. The headache shows a definite ten-

dency to be localized and develops usually above, behind or in the affected eye. The recurrence of the disorder is much more variable than in the other types of migraine. It is much more apt to be followed by permanent sequelæ. All of the cases which have been investigated at autopsy have shown localized lesions in or near the affected nerve and this constant finding of organic pathological change in ophthalmoplegic migraine would definitely suggest that it is not similar to simple migraine which so far as is known is a patho-physiological disorder. These facts would tend to throw some doubt upon the wisdom of including the ophthalmoplegic type of the disorder in the general group of migraine. Evidently a similar mechanism must be operative in the production of many of the symptoms but this does not mean that the underlying basis is the same in the two instances.

The other type of migraine which was unreservedly accepted by the older writers but which has been challenged by later and perhaps more critical consideration is facioplegic migraine. This form of the disorder is characterized by a recurrent paralysis of the seventh nerve of one side or the other, associated with discomfort within the head. In the majority of the reported instances the establishment of an independent type to accommodate such cases cannot be justified and apparently they represent only isolated or recurrent attacks of facial paralysis associated with more than the usual amount of head-pain. While it may be impossible at this time to state definitely that there is no type of migraine in which the innervation of the face is involved and that there is no such clinical entity as the facioplegic type of migraine it is perhaps wise to withhold any definite decision and await further and more definite reports of disorders of this kind.

The mass of evidence is so overwhelming concerning the appearance of migraine in families and in parents and descendants that it may be accepted as proven. Many investigators believe that in any family where migraine has developed 90—100 per cent of all the descendents will show some sort

of inherited tendency to migraine or one of the many disorders associated with migraine.

The inheritance factor in migraine is closely linked with the tendency to the development of other paroxysmal manifestations. Investigations have shown that migraine in the antecedents is more apt to produce convulsions in the descendents than the actual occurrence of convulsions in the parents. The inheritance factors have not as yet been definitely established and it is not clear whether there is a direct sex-linkage in the inheritance. The Mendelian character of the inherited tendency, whether dominant or recessive is also equally uncertain. The inheritance of migraine seems to be linked in some definite although intangible manner with the transmission of asthma, hay fever, urticaria and eczema.

Except in instances where migraine is closely associated with the menstrual function the recurrence of the attacks tends to be rather irregular. The attacks may occur as frequently as once or twice a day or they may only appear two or three times during the life of the individual. It has been estimated that in 82 per cent of the cases the attacks occur about once a month and in 52 per cent every two weeks or more frequently. In many instances there seems to be a definitely immune period following the attack during which time the disorder does not recur, but on the other hand the attacks may become so frequent that a *status hemicranicus* may be established. The occurrence of the disorder is most frequent between 18 and 35 years of age. It may appear, however, at any age epoch.

Until recently the disorder was considered to be much more frequent in women than in men. Investigators have stated that it occurs four times as frequently in women as it does in men. This preponderance in the female has, however, been questioned of late and figures have been presented which show the actual incidence of the disorder is about equal in the two sexes. The disparity noted in other investigations has been attributed to the fact that migraine is

apt to be more severe in women than in men and that women are more prone to seek relief than are the male members of the family. No especial influence seems to be exercised by occupation or other general factors. It may be stated that it is more apt to occur in those who live a confined life and in individuals whose activity is chiefly mental. The conditions described as predisposing or activating the attacks are so general in character that no importance can be ascribed to any of them.

The attacks of headache may develop with practically no warning or there may be a period of varying duration in which there are vague prodromata. Chief among these are a feeling of depression, lack of well being, and diminished energy. There is usually some reduced capacity for work or the patient may be irritable or restless. Certain authors have stated that the attack is preceded by a period of time in which the patient feels particularly well.

The headache may be generalized or may develop in one part of the head and radiate to other regions of the head, face, neck, shoulders or even to the upper extremities. It usually becomes more and more intense until the patient is incapacitated. It has been described as the pressure of a boring instrument or a feeling of distension within the skull as if the bones of the head would spring apart. Almost invariably the headache is associated at some time during its course, usually toward its termination, with nausea and vomiting. There are frequently other evidences of disturbance in the vegetative nervous sphere characterized by vasomotor alterations in the face and head or by actual hemorrhage from the retina, the mucous membrane or parts of the skin. There may be other local sympathetic disturbances leading to a feeling of coldness in the extremities, the appearance of goose flesh and other pilomotor phenomena together with excessive perspiration. The vegetative nervous system control of the organs of the chest and abdomen may become disturbed with the development of definite symptoms attributed to the heart, lungs, gastrointestinal tract, liver and other abdominal viscera. This

type of disturbance may even extend to the organs of the pelvis.

In the course of the attack, motor symptoms either of an irritative or paralytic character may present themselves. These evidences of abnormal nervous discharges may be localized or may be widespread. The usual disturbance is a paresis or actual paralysis of one or more of the limbs. This disturbance may change from one side to the other or may extend from an upper to a lower extremity or vice versa. Evidences of disturbance in some of the localized cortical motor activities may manifest themselves as an aphasia or an agraphia. A specialized type of motor disturbance may appear characterized by strictly cerebellar symptoms in which there is difficulty in equilibration and a definite disturbance in the synergic activity of the cerebellum. This type has been called hemicrania cerebellaris.

Disorders of sensation have also been described. The most constant of these is a feeling of tingling or numbness in one or another of the extremities or parts of the face, lips, tongue or mouth.

Disturbances of the special senses, exclusive of the visual function, are much less likely to make their appearance. Vertigo, tinnitus or diminution of hearing may appear. Hallucinatory disturbances of sight or hearing may take place while alterations in smell have occasionally been described.

In many instances a definite relation between the side of the headache and the presumed site of the development of symptoms has been noticed, the headache occurring on the side of the brain which is involved and therefore being opposite to the side in which the motor or sensory symptoms are manifested.

While the termination of the attack may be sudden, in the great majority of instances it is gradual and prolonged over a considerable length of time, the discomfort gradually diminishing, the symptoms declining in their severity and the patient slowly returning to normal.

The attacks may be followed by a more or less prolonged disturbance of function. In instances where the attacks are severe or rapidly repeated the residual phenomena show a greater tendency to become permanent. These sequelæ almost uniformly affect the structures whose functions are primarily attacked during the migrainous seizure. The occurrence of permanent sequelæ is usually attributed to the development of vascular lesions of one kind or another. In many instances a progressive arteriosclerosis with a gradual obliteration of the lumen of the vessel seems to explain the permanent loss of function. In other instances frequently repeated vaso-spasm seems to gradually reduce the viability of the cells which the vessel should nourish, with a gradual extinction of their function.

A considerable number of theories have been elaborated to account for the causation and to explain the varied manifestations of the disorder.

The Reflex Theory

The reflex theory is based upon the assumption that the migrainous attack results from the presence of a source of irritation somewhere within the body. The only one of these sources of irritation which has attained any degree of acceptance is prolonged eye-strain. With uncorrected refractive errors or conditions of improper illumination it seems definitely determined that such abuse of the eyes may result in attacks of migraine. It is self-evident that this cannot be the only cause for the attacks and that some tendency inherent within the disorder must be present to enable the eye-strain to produce its results. Too many individuals suffer from uncorrected refractive errors, and too many individuals with perfectly normal eyes have migraine to make it possible to explain all cases of migraine upon this basis.

The Central Theory

The central theory of migraine would explain the attacks upon direct, general or local changes in pressure or abnormal conditions of pressure within the cranial cavity. The

cavities of the brain, the brain substance itself and the coverings of the brain, including the skull, have all been blamed for the development of the attacks on the basis of some central change in pressure or other irritation. A critical examination of the foundation for this theory does not satisfactorily explain the recurrent and often periodic character of the disorder, neither does it make clear any mechanism which could bring about the changing manifestations of the attack. None of the symptoms, not even the headache, can be explained on the basis of this theory. The objections which can be raised to this theory are insurmountable and it is apparently impossible to explain the various manifestations of the disorder upon such a purely mechanistic conception as this central theory.

The Allergic Theory

A connection of some kind between attacks of migraine and allergic processes has been postulated by many investigators. The association of migraine with disorders of a demonstrated allergic character, such as hay fever, eczema, urticaria and asthma, the production of skin reactions by the action of known allergens and the elimination of attacks by careful attention to diet and desensitization, provide a firm basis for the assertion that some instances of migraine are due to allergic processes. The appearance of an eosinophilia which has been reported by numerous investigators would also substantiate this view. While the allergic theory offers hopeful and suggestive possibilities there must remain a definite reserve against the attempt by some investigators to explain all cases of migraine upon this basis.

Only a certain number of patients present a definite skin sensitivity, only a very few react specifically to food allergens, in many the diet may be reduced to not much more than one constituent without influencing the attacks, so that at present it is not justifiable to claim that more than a certain number of cases may be demonstrated to be allergic in character.

The Duodenal Stasis Theory

The role of the gastro-intestinal tract in the causation of migraine, has been emphasized by many investigators. A considerable amount of collateral evidence has been adduced to show that there is some demonstrable change in the gastro-intestinal tract or the biliary apparatus in certain cases. Reports, however, of an entirely negative character have also been placed on record and it must therefore be concluded that marked disturbances in the activity of the gastro-intestinal tract and its related organs may only be coincidental with the migraine. Very little direct evidence of disturbed gastro-intestinal function, demonstrated by means of fluoroscopic or x-ray examination has been brought forward. Perhaps the most that can be said at the present time is that a disordered activity of the gastro-intestinal tract, the liver particularly, may give rise to toxic products which may act in some not as yet understood manner as the detonator capable of producing attacks in a susceptible individual. An appreciation of the fact that toxic processes are called upon to explain every abnormal activity for which there is no demonstrable basis does not increase the confidence to be placed in this theory. The universality and ubiquity of toxic processes and materials makes it difficult to understand why everyone does not suffer from migraine and from every other sort of disorder. Even a very tentative acceptance of such a theory at once throws into relief the other essential factor, that is, the inherent, probably hereditary tendency which must be present in order that the toxic substance working in its presence shall be able to eventuate in the characteristic attack.

The Endocrine Theory

The two glands of internal secretion which have been considered most seriously as closely related to the production of migraine are the hypophysis and the gonad.

Many clinical considerations have suggested the connection between the crisis and these two incretory glands. The

remarkable temporal coincidence between migrainous headaches, menstruation and the cessation of the headaches during pregnancy, lactation and after the menopause has been recognized for centuries. The relation between gonadal activity and migraine is much more dramatic in women than in men, but its cessation after radiation of the testicles in certain instances may indicate that a similar relation is present in men also.

The other gland of internal secretion which has been implicated in the production of migraine is the hypophysis. The role of the gland in the migraine mechanism may be played through pressure of the enlarged gland upon the surrounding structures or through disturbed hormonal relations or both. The anatomical location of the hypophysis supplies a most attractive basis for the supposition that an increase in the size of the gland can directly affect structures which could produce practically all of the symptoms of migraine. The restriction of the gland within the walls of the osseo-membranous space, the pituitary fossa, could explain the headache and the nausea and vomiting, the optic chiasm and tracts lie immediately above rostrally and laterally, and pressure upon them could be responsible for the visual symptoms, the carotid artery and its branches, the anterior and middle cerebral arteries are directly lateral and somewhat ventral and a circulatory interference in them could explain many of the symptoms coming from the cortical areas, while pressure upon the floor of the third ventricle or a disturbance in its neural connections could explain all of the vegetative nervous symptoms. A number of general considerations such as craving for sweets, a low blood sugar, polyuria, the occasional appearance of acromegaly and the observation that activities which call forth an unusual hypophyseal activity are identical with those which may precipitate an attack, such as over-exertion, hunger, fatigue, etc. seem to link the hypophysis with migraine. Certain investigators have demonstrated, post-mortem, an asymmetrical position and a tendency on the part of the hypophysis to encroach upon the

carotid artery and the cavernous sinus in patients who had suffered from migraine. Unfortunately for their theory, these conditions were not limited to migraine. Other investigators have demonstrated unusual and abnormal calcification in the region of the pituitary fossa.

In an investigation of the hormones of the hypophysis and the ovaries now being carried on at the Neurological Institute and the College of Physicians and Surgeons, it has been found that theelin, the ovarian follicular hormone is either markedly reduced or absent whereas prolan the hypophyseal hormone is almost regularly present in the urine of patients suffering from migraine. This is a condition found heretofore only in pregnancy, after the menopause and with certain neoplasms of the genital tract. In following the excretion of these hormones, it was found that the amount of prolan was regularly increased a day or so before the onset of the migrainous attack. These observations are apparently the first factual evidence connecting the hypophysis, the ovary and the migrainous attack. Further investigation will be necessary to discover the many other links in the chain, but these facts would seem to substantiate fully the assumption that some part of the mechanism of migraine is dependent upon the interaction of the hypophysis and the ovary.

The Vasomotor Theory

The theory which will most satisfactorily explain directly many of the features of the migrainous seizure is the one which is based upon the activity of the vegetative nervous system in the production of local constriction of the blood vessels. The character and the appearance of the symptoms, the very evident disturbances of circulation in the head and other parts of the body, the demonstration of a disturbed circulatory reaction to scratching the skin, the transient character of the attack and the development of sequelæ can all provide evidence which closely associates the disorder with a disturbed vasomotor control. The participation of the vegetative nervous system and its vaso-

motor control while not in itself sufficient to explain the entire picture is probably one of the links in the pathophysiological process which results in migraine.

Perhaps a combination of the endocrine and the vasomotor theories presents the best basis available to account for this kaleidoscopic symptom-picture. This hypothesis would presuppose an irritability of the vasomotor system which is at time aroused into abnormal activity by a change in the relation between the circulating hormones. The facts presented showing that there is a distinct imbalance or a disordered relation between the products of the internal glands is a very suggestive bit of evidence substantiating this hypothesis. The remaining links in the chain are as yet undetermined. This field is a very profitable one for further investigation.

The present status of the metabolic and biochemical investigation of patients suffering from migraine is unsatisfactory. No group of patients of sufficient size has been investigated with enough thoroughness to establish any absolute conclusions as to the condition of the body fluids. The great majority of investigations have been confined to special fields and the groups examined have been uniformly small.

The repeated investigations of the urine have been barren of any satisfactory or significant results. The only real deviation which has been recorded is a diminution in chloride excretion during the premigrainous period. It has been claimed that a pentosuria frequently accompanies the attack.

No definite changes in the blood have been recorded except the appearance of an eosinophilia as high as 15-16 per cent and also the appearance of an increased amount of cholesterin. This eosinophilia was reported in a group of patients presenting marked sensitization and is not corroborated by other observers. The cholesterinemia has been demonstrated to reach 300 mgm. per 100 c.c. of blood, the normal value being about 210 mgm. Except for these varia-

tions no definite alteration in the morphology or chemical constitution of the blood has been established by any investigator.

The examination of the spinal fluid both during the interval and during the migrainous attack, the investigation of the basal metabolic rate and the estimation of the blood pressure have been equally unproductive of significant values.

X-ray examination of the skull by certain investigators has demonstrated definite changes, particularly in the development of abnormal ossification or calcification in the interclinoid ligaments and also other evidences of abnormal bone formation in the region of the sella turcica. These changes have also been found in patients not suffering from any known disturbance of the central nervous system. Their exact relationship, therefore, to migraine does not yet stand as proved.

In regard to the morphological constitution of patients suffering from migraine no significant conclusions have been reached. No group of cases sufficiently large to warrant an authoritative pronouncement has been studied. Any relation between the morphologic constitution and this disorder has not been demonstrated. Investigations have shown the co-existence of numerous abnormalities in morphological development not only in the bones but also in the soft tissues. However, these anomalies are those which might well be found in any large group of individuals suffering from any disorder.

The contributions of general pathology to the understanding of migraine, exclusive of the ophthalmoplegic type, are negligible. As has already been mentioned, autopsies have been performed on a considerable number of patients who had suffered from ophthalmoplegic migraine and in these instances definite pathological alterations have been found in the vicinity of the oculomotor nerves or involving the nerves themselves. These have principally been neoplastic formations on or about the nerves. Asser-

tions have been made that in migraine there exists an abnormal relation between the hypophysis and the surrounding structures. The applicability of this assertion to migraine is, however, greatly weakened by the further statement by the investigator that this same situation was found to exist in a miscellaneous group of conditions such as hysteria, convulsive disorders, general paralysis and melancholia. Only one or two reports of autopsies performed on patients who had suffered from migraine have appeared in the literature. These reports are entirely devoid of significant conclusions which could be connected with the disorder. The careful pathological investigation of patients who had suffered from migraine is of essential importance. In any such investigation the exact relationship of the hypophysis to the surrounding structures, the minute condition of the vascular tree and especially the condition of the vessels supplying areas which have shown definite focal symptoms and the histological appearance of the cells in these areas must be exhaustively studied before any conclusions may be reached as to the pathology of the disorder.

Treatment

Practically every known form of therapy has been tried by clinicians in the attempt to remove the causative factors of migraine or to alleviate the symptoms. The number and diversity of the therapeutic agents which have been used in the handling of these patients would indicate the nonspecific condition of therapy in the disorder. Almost every report containing the results of treatment hails the brilliant results obtained by some favorite therapeutic agent; each separate form of treatment is successful in the hands of the individual therapeutist and no one has yet reported any consistent group of failures. The majority of the reports are based upon relatively small groups of patients.

There are a number of general principles to be considered and applied in the management of migraine. The essential basis for treatment is the differential diagnosis. Every patient suffering from migrainous attacks should be

thoroughly examined systemically and neurologically. The eyes and spaces associated with the nasal cavities should receive adequate investigation. Eye-strain or other ocular disturbance and unsuspected disease of the accessory spaces of the nose are often the cause of symptomatic migraine; they must be eliminated before the condition can be considered as a true migraine. The patient should then receive a thorough investigation by means of a laboratory study if possible.

The warning of Tzanck that one must be cautious in estimating the results of any definite kind of therapy, since any material change in almost any direction in the patient's regime is apt to be followed by at least temporary improvement can be appropriated as a therapeutic principle. Some definite change should be made in the life habits of the patient suffering from migraine if it is in any way possible. This should apply to his work, his play, his food, his mental attitude and his philosophy of life. Glaring inequalities of emphasis in the patient's interests and activities should be corrected and his manner of life made as rational as possible. Excesses in all directions should be curbed. The salutary effect of exercise especially for the sedentary patient cannot be over-emphasized and any outline of treatment must always take full cognizance of this feature. Rest and change must also be enforced for those under material physical, mental or emotional pressure. The importance of regular holidays, vacations and time off during the day or the week should be stressed.

The management of the acute attack does not present much opportunity for therapeutic effort except along the lines of medicinal therapy. The patient is so intensely uncomfortable that usually he will not tolerate any mechanical procedures and often will not even allow himself to be approached by nurse or doctor. The room should be darkened and the entrance of stimuli of any kind whatsoever reduced to a minimum. An ice-cap to the head and hot-water bottles to the feet or hot mustard foot baths sometimes seem to relieve the intensity of the attack.

The nausea, vomiting and retching can frequently be controlled or at least reduced by glucose enemata. A warmed 10 per cent solution of glucose, in quantity from 5 to 10 ounces, can be introduced into the rectum every two hours or so. To the enema may be added 20 to 40 grains of bromide and 10 to 20 grains of chloral hydrate. If the larger quantities of the drugs are used, the enemata should not be repeated more frequently than every three hours. Sodium luminal by hypodermic, in one or two grain doses frequently diminishes the tendency to nausea and vomiting. No foods or liquids should be given during the period of acute emesis. Cracked ice may be allowed to melt in the patient's mouth.

The special therapeutic procedures are principally used in the interval treatment and may be separated into a number of groups.

In view of reported gastro-intestinal and biliary disorders it is wise in all cases which show any functional disturbance of these organs to direct the treatment toward them. The principle measure to be adopted is, of course, dietetic. Aside from dietary regulation the chief procedure which has been suggested is intraduodenal lavage with infusions of 33 1/3 per cent magnesium sulphate. From two to four ounces may be introduced through a duodenal tube. The result is to produce an active flushing of the duodenum and of the biliary passages by means of the fluid drawn from the circulation by the presence of the magnesium sulphate in the duodenum. This method of treatment has met with great success in the hands of those who have used it. Other investigators have advocated an even more vigorous attack upon the intestinal tract including duodenojejunostomy and other operative procedures; but these more radical methods of treatment are not to be advised unless the condition of the gastro-intestinal tract itself makes operative interference necessary. The presence of the migraine alone is not sufficient justification for such extensive surgical procedures.

Non-specific protein therapy is advocated by a considerable number of investigators. The purpose of this treat-

ment is to produce a hyperthermia which has been said by some mysterious alterative effect to influence the underlying basis for migraine. A number of materials have been suggested for this form of therapy. The injection of autogenous whole blood or serum has been advocated. The technic includes the withdrawal of 20 c.c. of blood and its immediate reinjection either subcutaneously or intramuscularly or the serum may be injected after coagulation. The use of old tuberculin in doses varying from 1/10, 000,000 to 1/1,000,000 at first twice a week and later once a week has been advocated by a number of clinicians. Those who have used this method of treatment report that its use has resulted in material improvement in many instances and cure in a number of cases. Peptone has also been used either by mouth or by intravenous injection. Armour's peptone, 0.25 c.c. of a 5 per cent solution increasing by 0.25 c.c. until a maximum of 1.25 c.c. is reached, has been used with quite satisfactory results.

Other authors have injected typhoid vaccine intravenously beginning with 2½ million bacteria and increasing the dose according to the results obtained. Other similar therapeutic agents such as aolan, hyperthermin, vaccinurin and "cewega," a crystalline plant protein, have been used successfully in the production of transient fever. The use of cholin, an oxidation product of cholic acid has also been tried in doses of 0.25 gram twice a day, the dosage being reduced after the second and third week and then continued for an indefinite period. None of these methods, however, apparently results in any permanent cure of the migrainous state and the notation constantly recurs that after the treatment has been interrupted it is necessary to repeat the series of injections.

The dietetic treatment of migraine follows three general principles:

1. Non-specific diets; 2. Non-allergic elimination diets; 3. Ketogenic diets.

According to the special predilection of the particular in-

vestigator any of the constituents of the diet, protein, carbohydrate, fat, water, mineral salts, may be modified in the attempt to prevent the recurrence of the migrainous attack. It is, of course, self-evident that in patients who present an unhealthy condition of the intestinal tract definite steps should be taken toward the improvement of this phase of the situation. The advocates of the restriction of this or that constituent of the diet have almost universally reported good results. Where there is a tendency toward the development of putrefactive processes those articles which increase this condition should be eliminated and the production of gas reduced to a minimum by the restriction of fats and carbohydrates.

Dietary restriction in the treatment of migraine may be strikingly successful. The decision as to the actual type of dietary control to be exercised will depend to a considerable extent upon the condition of the patient and his general make-up. It is along the lines of dietary control that a definite change can be made in the patient's general metabolism and thus produce the critical alteration which may diminish or prevent the attacks. The obese sedentary individual should be placed upon a reducing diet and regime and no effort spared until a steady, reasonable reduction in weight results. The spare thin overactive individual should be placed upon a high caloric diet with a regime containing enough rest to allow the deposition of a reasonable amount of reserve flesh and adipose tissue. For the patient who eats nothing but fats or carbohydrates should be prescribed a balanced diet containing proper quantities of these constituents.

The results obtained by the identification and elimination of specific allergens is often most dramatic and most satisfactory to the patient. If there is any suspicion of a sensitization in the patient a careful and systematic search should be made by those competent to handle this sort of an investigation. Not only the routine skin tests but also where indicated the elimination diets should be used. Many observers believe that from 30-50 per cent of patients suffer-

ing from migraine can be relieved by the elimination of these allergens. Few individuals suffering from migraine can eat meat, fish, eggs, and other animal proteins in any quantities. The various allergens which have been found to be definitely prone to produce the attack of headache are those contained in sweetbreads, eggs, milk, mushrooms, tomatoes, oranges, shell-fish and chocolate. Few therapeutic results can be more pleasing than the elimination of the migrainous attack through the removal of the guilty article from the diet.

Brilliant results have been reported by many investigators who have attempted to control the disorder by the ketogenic diet. Certain other investigators who have conscientiously tried this treatment report that they could not convince themselves that any favorable results followed its use. The good results obtained by some authors were attributed by others to the effect of the excessive fat favoring the emptying of the gall bladder, biliary passages and the peristaltic action of the duodenum also was supposed to be improved. The beneficial effect upon the migraine was attributed more to the improvement in the general intestinal hygiene than to the specific action of the diet. Certain investigators who have followed the degree of ketosis and the clinical state of patients report that there is no relationship between the ketosis, the amount of improvement in the patient or the actual recurrence of the migrainous seizure. Whatever the actual cause the ketogenic diet does seem to be of value in certain cases of migraine.

The alleviation and cure of the attacks of migraine has also been attempted by means of surgical therapy. Three modes of surgical treatment have been advocated:

1. The removal of certain sympathetic ganglia, 2. The ablation of some of the vascular plexuses of the sympathetic, 3. The occlusion of the middle meningeal artery.

In several instances where occlusion of the middle meningeal artery has been produced surgically prompt relief

from the migrainous seizures has been obtained. This form of therapy has, however, been introduced only recently and a sufficient length of time has not elapsed for the establishment of definite conclusions. The other procedures advocated are certainly serious and in certain instances extremely radical. Some of the reported cases indicate the apparent removal of the entire cervical sympathetic chain and as much of the thoracic chain as lies within reach of the surgeon. The reports of the results are too few and many of the reports too recent to allow for the test of time. Every other method of treatment should be exhausted before recourse to surgery is attempted.

Glandular therapy has always been most popular in the treatment of migraine. The evident relation between migraine and the ovaries and hypophysis as outlined under the endocrine theory of the causation of migraine has supplied ample basis for endocrine treatment. Many clinicians have advocated the treatment of migraine by means of pituitary extract. Many preparations are recommended and administration has been by mouth and by hypodermic injection. Extracts of the anterior lobe are principally used but many authors prefer to use the whole gland. Numerous clinicians have reported the elimination of the attacks by the use of pituitary extracts, particularly when the headaches were strictly menstrual in occurrence.

Similar good results have been recorded by an equally large number of observers who have treated this disorder with ovarian extracts. Quite satisfactory results seem to follow the use of ovarian, follicular or corpus luteum extracts. Striking results have followed the use of progynon, a female sex hormone obtained by extraction from the placenta. This is preferably given by hypodermic injections at first, the tablets being substituted after ten or twenty injections. The tablets are given by mouth three times a day, the hypodermic injection three or more times a week. Very satisfactory results have been obtained by the use of theelin, the follicular sex hormone which can be given by vaginal suppository, by injection or by mouth as theelol.

An extensive series of treatments with theelin is now being carried on at the Neurological Institute, but no report is ready as yet.

Many investigators have recommended the destructive radiation of the gonads by x-ray or radium and many cures of the disorder by the production of an artificial menopause have been reported. Other authors have advised the surgical removal of the testicles or ovaries.

The treatment of migraine by means of drugs may be divided into two phases:

1. Treatment during the interval.
2. Treatment of the acute attack.

Only a few drugs have been proposed for continuous use over any considerable length of time. On account of the evident relation of migraine to the convulsive state many authors have advocated the protracted use of luminal. The general impression is that luminal, of inestimable value in the treatment of convulsive disorders, is not so specific in migraine. Luminal should be given in maximum doses of ½ to ¾s of a grain three times a day. In this dosage, luminal was used in thirteen cases of migraine at the Migraine Clinic in the Vanderbilt Clinic; seven cases were markedly improved, one improved and five cases remained uninfluenced by the drug. Its use may be continued over considerable lengths of time without any appreciable loss of efficacy.

Ephetonin, a synthetic racemic substitute for ephedrin and ephedrin itself have been used successfully by a number of investigators. If ephedrin is used, it should be prescribed as one to two teaspoonsful of the Elixir of Ephedrin Hydrochloride two to three times a day.

On the basis that the disorder is due to a calcium deficiency, a number of investigators have attempted to control it by means of the daily intravenous injection of 10 per cent solution of calcium chloride. Other intravenous preparations of calcium were also used. As is the case with almost

everything suggested or advised in the treatment of migraine, the use of calcium has met with quite satisfactory results. While in certain instances it must be continued indefinitely, in a certain number of cases the tendency to a recurrence of the disorder has been apparently interrupted.

In the treatment of the acute attack a considerable number of drugs have been recommended. The caffein group has been used extensively and black coffee is one of the most popular agents for the prevention and cure of an attack. A number of proprietary drugs with one or another of the caffein group as the principal ingredient have been placed upon the market, each one meeting with a modicum of success. In almost all instances caffein is combined with one or another of the coal-tar products. Caffein in doses of one quarter to two grains, acetanilid, 2 to 3 grains, phenacetin, 3 to 5 grains, sodium salicylate, 1 to 5 grains, monobromated camphor, ½ to 2 grains, the extract of hyoscyamus, 1/8 grain, tincture of gelsemium, 4 minim., have all been used in varying combinations. Probably one of the most successful combinations not only for the control of the migrainous headache but also in other varieties of discomfort in the head is the so-called Faivre's cachet of oxyquinothine. This is a trade name and the actual combination consists of phenacetin, acetanilid and caffein in the usual doses. Satisfactory results follow the use of one capsule every half hour for three doses and after that one every two hours if necessary. The administration of ergotamin tartrate, also called gynergen, has been suggested by a large number of authors in the treatment of the acute attack and also as an interval treatment. Ergotamin tartrate may be prescribed as 1 to 3 mgm. twice a day if used as an interval form of therapy. As the expected time for the migrainous attack approaches the dosage may be raised to six times a day or it may be administered by subcutaneous injection, 0.5 mgm., twice a day. For the control of the acute attack 2 mgm. by mouth or 0.5 mgm. may be given by intravenous injection and repeated in half an hour. The symptoms of intoler-

ance to the drug are palpitation, nausea and vomiting. If the subcutaneous route is used, the patient should be tested for an idiosyncrasy to the drug by giving a quarter or even an eighth of a mgm. Gynergen, 0.5 mgm., may also be combined with bellafoline in doses of 1 to 4 tablets daily or 0.5 c.c. hypodermically.

Blood pressure reducing principles such as nitroglycerin and nitromanite have been used. Nitroglycerin should be prescribed in doses of 1/50 of a grain by mouth or 1/100 of a grain by hypodermic and repeated every half hour. Erythrol tetranitrate in one grain doses may be efficacious.

The two drugs most widely used for the control of the more intense form of the headache are, of course, codeine and morphine. In many instances codeine by mouth or by hypodermic injection is sufficient to abort or terminate an attack. When efficacious by mouth it should be given by this route. If codeine is not sufficiently strong to control the attack, recourse must be had to morphine. In sufficient doses it will alleviate the agony of the most severe migrainous headache and it should be used in adequately large doses and frequently enough to accomplish results. It must never be overlooked, however, that until the cause for migraine is found and controlled one is dealing with a recurrent disorder and therefore the danger of drug addiction must be avoided at all costs. Morphine should not be used until it becomes evident that the headache is to be definitely severe and it should not be used more frequently than is essential. There is no object to be gained, however, by giving inadequate doses.

The treatment of migraine presents an extreme diversification of therapeutic measures. In view of the satisfactory results obtained by many divergent methods it is apparent that the mechanism of migraine may be influenced from many sides. The wide range of these procedures makes it almost impossible to draw any satisfactory conclusions. The real therapy of the condition must await the identification of the mechanism for the attacks. At

present therapy in the acute attack is directed toward the relief of what appear to be vascular crises. The treatment during the interval should be directed toward the rectification of any abnormal tendencies in the individual. At present, our efforts at the clinic are being directed along the lines of organotherapy. Our investigations have shown a definitely altered condition of hormonal balance. Our therapy consists of the use of theelin, either as vaginal suppositories or by hypodermic injections. The results of therapy are encouraging and will be fully reported at some later date.

The list of references used in the preparation of this article can be found in the Bulletin of the Neurological Institute Vol. II. No. 3, November 1932.

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